Case Management of Malaria in Pregnancy

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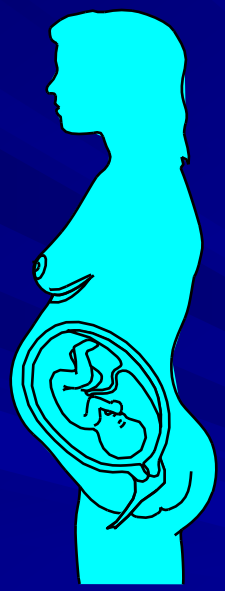
Contraindicated Drugs

- **Tetracycline**
- **Doxycycline**
- **Primaquine**
- **Tafenoquine**
- **Halofantrine**



Drugs thought to be safe

- Azithromycin
- Chloroquine
- Clindamycin (usually paired with quinine or quinidine; rarely used in Africa)
- Dapsone
  - (+ pyrimethamine = Maloprim)
  - (+ chlorproguanil = Lapdap)
- Mefloquine (prophylaxis)
- Proguanil, chlorproguanil (usually paired with other drugs)
- Pyrimethamine (usually given as SP)
- Quinine, quinidine (risk of hypoglycemia)
- Sulfonamides (usually given as SP)

Drugs with questionable safety or limited data

- Amodiaquine (no data)
- Artemisinins
- Atovaquone-proguanil (Malarone) (limited data)
- Lapdap (chlorproguanil-dapsone) (limited data)
- Lumefantrine (component of Coartem) (no data)
- Mefloquine (treatment dose)
- Combination therapy
  - Amodiaquine-SP (no data)
  - Artemisinin derivative with other drugs
    - AS+SP; AS+AQ; piperaquine + dihydroartemisinin; lumefantrine+artemether.

Newman et al, *Tropical Medicine and International Health*, 2003

Management of uncomplicated malaria in pregnancy

In areas with CQ and SP resistance (Kenya)

- **1st trimester**
  - **Quinine 10mg salt three times daily + clindamycin* (10mg/kg twice daily) for 7 days.**
- **2nd and 3rd trimester**
  - **ACT known to be effective in the region (ART/LUM , AQ/AS) OR**
  - **Artesunate plus clindamycin* (10mg/kg twice daily) for 7 days OR**
  - **Quinine plus clindamycin* - both drugs given for 7 days**
- If clindamycin is unavailable or unaffordable then quinine monotherapy may be given

Artemether-lumefantrine in pregancy

- Artemisinins associated with teratogenicity, embryolethality, and foetal death in rats and rabbits
- Teratogenic effects include neuro, cardiac anomalies
- More time of exposure related than dose related
- No effects as yet reported in 30 million doses of human use
- Data on early pregnancy exposure in non-human primates being evaluated
- Pregnancy register established in Zambia to monitor effects of inadvertent exposure in pgcy
- Comparative clinical trials in Thailand with SP to enroll 1600 patients, 1200 taking AL in $2^{nd}/3^{rd}$ trimester
- No data available on lumefantrine effects, use AL only in 2nd and 3^{rd} trimester

Management of severe malaria in pregnancy

- All trimesters (save mother's life at all costs)
  - Parenteral quinine +/- clindamycin
  - Parenteral artemisinins +/- clindamycin
- In intensive care – high rate of maternal and periantal mortality
  - Fluid management
  - Prevention / treatment of hypoglycaemia
  - Management of premature labour or just labour
  - Management of severe anaemia (pulmonary oedema may occur)
  - Postpartum haemorrhage and risk of death very high

Conclusion

- Malaria in pregnancy is a big cause of maternal and perinatal morbidity and mortality
- There are gaps in knowledge concerning
  - development of immunity to malaria,
  - *P. vivax* infections in pregnancy
  - Effective therapies for both IPTp and case management
- Programs for the control of malaria in pregnancy have not yet been widely and successfully implemented.

WHO recommendations

- Areas with <30% PF at Day 14
  - Implement IPT with at least 2 doses
  - ITNs, treat anaemia, case management
  - Evaluate impact of IPT
- Areas with 30 – 50% PF at Day 14
  - Implement or adopt IPTp policy
  - ITNs, treat anaemia, case management
  - Evaluate on ongoing basis
- Areas with >50% PF at Day 14
  - Emphasize control with ITN, anaemia and malaria management
  - CT IPT policy and evaluate
  - Consider adopting IPTp with SP when evidence of efficacy for IPT available in setting

WHO/AFRO/MAL/MIP.IPT/05

SP for IPTp precautions

- HIV infected pregnant women taking cotrimoxazole for prophylaxis should not receive IPT with SP
  - Study on efficacy of CTX on PAM on-going
- Do not give IPTp with SP to those allergic to sulpha drugs
- Gambia studies showed no effect of folate supplementation on efficacy of SP
- Recent data from Siaya however suggests that giving SP with high dose folate (1 – 5mg) does reduce its efficacy while 400µg does not*

**Ouma P et al (2006) PLoS Clin Trials 1(6)*

IPT future thoughts

- Increasing *P. falciparum* mutations to the *DHFR* gene
- Of 5 mutations, 164 is rarest and confers total resistance to all anti-folates
- Approx: 25% in Thailand, detected in western Kenya
- Implications for use of candidate drugs for IPTp such as chlorproguanil/dapsone, atovaquone/proguanil +/- artesunate

ITNs during pregnancy: summary

- Variations in study design (gravidity, end point, randomization)
- Some heterogeneity in efficacy estimates
- ITN effects
  - Reduce maternal malaria and placental malaria
  - Reduce maternal anemia
  - Increase mean birth weight
- No effect modification by transmission intensity
- Effect smaller than with IPT
- **Take home message: ITNs do prevent adverse consequences of malaria during pregnancy, and should BE PART of a complete package in ANC**

IPTp and ITNs

- Combined effect of ITNs and IPT (SP)
  - Only one study (Njagi et al, western Kenya)
    - Both interventions effective
    - IPT alone >> ITNs alone
    - Little additional benefit from ITNs over IPT

Neonatal Malaria

- Age old teaching that mother's antibodies protective till at least 12 weeks
- Preventive measures – maternal immunity changes
- 0 – 12 weeks also susceptible to malaria and must be considered as DD when with fever
- IMCI?

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